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Major Congenital Malformations in Down Syndrome

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We studied major malformations in 5,581 infants with Down syndrome (DS) from three registers of congenital malformations. The prevalence at birth of 23 different malformations was compared with the program-specific rates for each malformation in non-DS infants. An about 300 times risk increase was seen for annular pancreas, cataracts and duodenal atresia and an about 100 times risk increase for megacolon and choanal atresia. Esophageal, anal and small bowel atresia, preaxial polydactyly, and omphalocele all showed risk increases between 10 and 30 times. Statistically significantly elevated risk ratios around 3–5 were seen for cleft palate, cleft lip/palate, and limb deficiencies. No increased risk was seen for neural tube defects, hydrocephaly, microtia, renal agenesis or severe dysgenesis, hypospadias or polydactyly other than preaxial. Oral clefts were more often present in DS in the Swedish material than in the other two materials. Cardiac defects were registered in 26% of all cases (varying between programs) but 28% of the cardiac defects were unspecified. DS infants born to women younger than 25 years had a significantly increased risk for megacolon and there was a trend of increasing risk for esophageal or anal atresia with maternal age. A decreased risk for cardiac defect in DS infants born to teenage mothers was found, quite pronounced for endocardial cushion defects and ventricular septum defects. There were no statistically significant differences in the sex distribution of specific malformations in infants with DS and in non-DS infants.

KEY WORDS: Down syndrome, congenital malformations, maternal age, sex

INTRODUCTION

The phenotype of Down syndrome (DS) is characterized by a number of minor anomalies such as simian creases, epicanthic folds, oblique palpebral fissures, clinodactyly, small head circumference, brachycephaly, and a flat face. Congenital heart defects are common. Acutis et al. [1983] found such defects in 33% of DS. It is also generally known that certain other major malformations are common, e.g., cataracts, duodenal atresia, and megacolon. We have collected a sample of 5,581 infants with DS using information from three registries of congenital malformations in Europe and compared the rate of certain common major malformations in DS with the rates in other infants. This is probably the largest detailed material from infants with DS collected until now.

MATERIALS AND METHODS

Information on infants born with a diagnosis of DS (aborted fetuses were not included) was collected from three registries: the Central-East France Registry is a regional, population-based registry with multiple-source ascertainment of cases and approximately 100,000 annual births. Data were obtained for 1976–1991. The Italy:IPIMC Registry is a hospital-based registry drawing data from 114 hospitals all over Italy (about 25% of all Italian births) and has approximately 130,000 annual births. Data were obtained for 1978–1990. The Swedish Registry is a national, population-based multiple source registry covering about 100,000 annual births. Data were obtained for 1978–1993. Further details can be obtained from an ICBDMS publication [1991].

For each DS subject, information was given as individual records according to a fixed record layout stating, among other things, infant or fetal sex, maternal age, gestational age, birth weight, and codes for major malformations. The latter were coded using the three-digit code introduced in the ICBDMS for the monitoring of infants with multiple malformations [Mastroiacovo, 1991] except for cardiac defects which were coded using the ISC code [International Society of Cardiology, 1970] when possible.

When an infant had more than one cardiac diagnosis, a hierarchic model was used, selecting the clinically most important one according to the principles in the New England registry of infants with cardiac defects

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[Fyler et al., 1980]. The actual hierarchy used is apparent from Table III.

Comparisons with population rates were made based on figures given in the ICBDMS [1991] publication. New data on population rates (during the relevant years) were collected from each program for cataracts, choanal atresia, duodenal atresia, other small bowel atresias, megacolon, annular pancreas, and different types of polydactyly (preaxial, postaxial, other, or unspecified). From these rates, the expected number of infants with DS and each type of malformation was calculated and the observed number was compared with the expected number as an observed/expected ratio, the exact 95% confidence intervals of which were based on Poisson distributions when the observed number was below 10, otherwise on normal approximations.

Maternal age distribution was compared between DS with specific types of defects and all other DS infants in the material, stratifying for program. Sex distribution was studied for each associated malformation and the sex distribution in DS with a certain malformation was compared with the sex distribution of that type of malformation in non-DS. As the total group of DS has a sex ratio different from that of the population, the comparison was made as two 2 × 2 tables: male/female versus malformed/nonmalformed, one valid for DS, the other for non-DS. Homogeneity between these two tables was tested with Breslow and Day tests. When no heterogeneity existed, a common odds ratio, stratified for DS/non-DS, was made in order to demonstrate the sex preponderance of a specific malformation (mainly determined by the non-DS individuals because of their greater number).

Tests of homogeneity in frequencies across programs were made using Breslow and Day tests and odds ratios were calculated with the Mantel-Haenszel procedure with test-based confidence intervals; at low numbers exact odds ratios with mid-*P*-corrected confidence intervals were calculated using StatExact software (CYTEL Software Corp.). The same program was used for trend analyses.

RESULTS

A total of 5,581 infants with DS was identified: 1,554 from Central-East France (1976–1991), 1,877 from Italy:IPIMC (1978–1990), and 2,140 from Sweden (1978–1993). Among them, the karyotype was not known in 1,696 instances (30%). Among the remaining ones, 3,678 (94.7%) were regular trisomy 21, 135 (3.5%) were translocations, and 71 (1.8%) mosaics. In the remaining case, there was an iso-21q karyotype. There is no information on paternal or maternal origin of the chromosome anomaly or which meiosis was involved in the nondisjunction process. No aborted fetuses were included in the material but 57 infants were stillborn.

Major Noncardiac Malformations

Table I summarizes the occurrence of 23 major malformations for which population data were available.

Figure 1 shows the relative risk to have each one of these malformations in a DS compared with the population rates, stratified for program. Some of the malformations (neural tube defects, hydrocephaly, microtia, renal agenesis/dysgenesis, hypospadias and nonpreaxial polydactyly) are compatible with a "normal" rate (risk ratio = 1). Cleft lip/palate and isolated cleft

TABLE I. Groups of Major Congenital Malformations in Down Syndrome Infants*

Defect	Monitoring program				Per 1,000 Down infants	Expected number
	France	Italy	Sweden	Total		
Anencephaly	0	0	0	0	0	1.0
Spina bifida	1	1	2	4	0.7	2.4
Encephalocele	0	0	0	0	0	0.5
Hydrocephaly	0	2	1	3	0.5	1.7
Cataract	5	7	4	16	2.9	0.3
Microtia	0	0	0	0	0	0.9
Isolated cleft palate	0	1	8	9	1.6	3.0
Cleft lip/palate	2	6	8	16	2.9	5.0
Choanal atresia	1	2	1	4	0.7	0.3
Esophageal atresia	15	19	11	45	8.1	1.6
Duodenal atresia	44	46	48	138	24.7	0.5
Other small gut atresia	0	8	0	8	1.4	0.4
Anorectal atresia	17	17	16	50	9.0	1.8
Megacolon	13	4	14	31	5.6	0.3
Annular pancreas	3	13	11	27	4.8	0.2
Kidney agenesis or dysgenesis	0	1	1	2	0.4	0.9
Hypospadias	2	1	7	10	1.8	9.7
Limb reduction defect	4	5	1	10	1.8	3.2
Diaphragmatic hernia	2	2	0	4	0.7	1.3
Omphalocele	5	3	0	8	1.5	0.9
Gastroschisis	2	0	0	2	0.4	0.4
Preaxial polydactyly	3	5	5	13	2.3	1.3
Postaxial or other polydactyly	0	1	0	1	0.2	2.9

* Numbers and rates, with comparisons with the expected numbers, based on population frequencies and stratified for program.

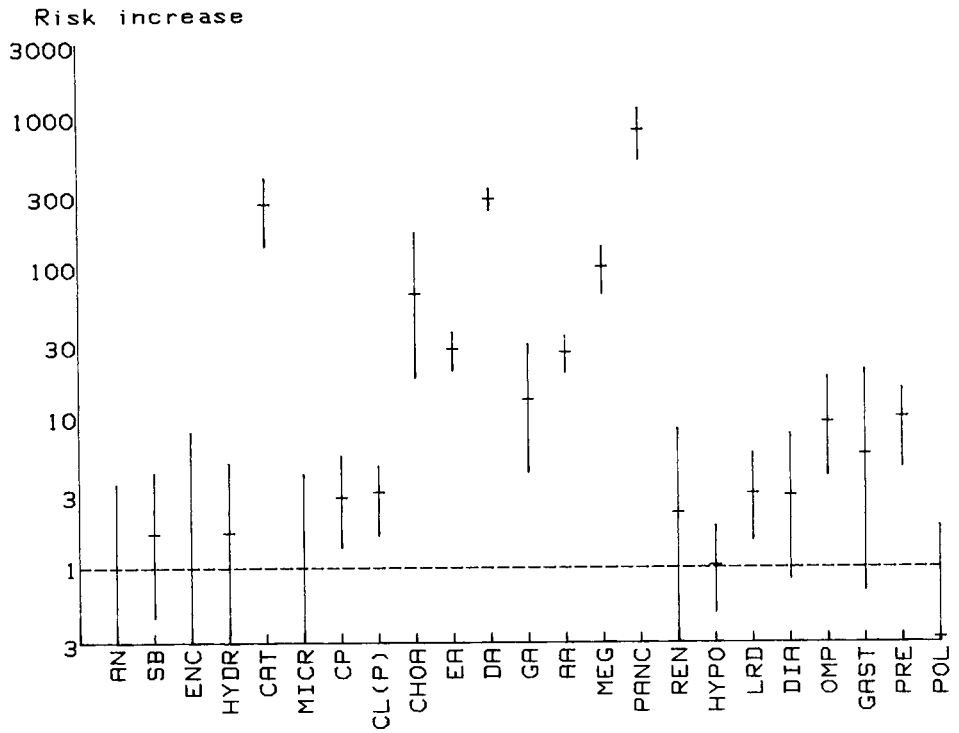

Fig. 1. Diagram showing relative risk for specific malformations in infants with Down syndrome compared with non-Down syndrome infants after stratification for program. Risk ratios are shown with 95% confidence intervals from exact Poisson distributions. AN, anencephaly; SB, spina bifida; ENC, encephalocele; HYDR, hydrocephaly; CAT, cataract; MICR, microtia; CP, isolated cleft palate; CL(P), cleft lip with or without cleft palate; CHOA, choanal atresia; EA, esophageal atresia; DA, duodenal atresia; GA, other small bowel atresia; AA, anal atresia; MEG, megacolon; PANC, annular pancreas; REN, renal agenesis or severe dysgenesis; HYPO, hypospadias; LRD, limb reduction defect; DIA, diaphragmatic hernia; OMP, omphalocele; GAST, gastroschisis; PRE, preaxial polydactyly; POL, other polydactyly.

palate, limb defects, and diaphragmatic hernia show a 3–5 times increased risk, all except diaphragmatic hernia with lower confidence intervals well above 1.

The highest risk ratios were found for cataracts, duodenal atresia, megacolon, classical malformations associated with DS. Also markedly elevated risk ratios, although not so high, are found for choanal atresia, esophageal, anal, and ileojejunal atresia (13 to 29 times). There is a marked increased risk for preaxial type polydactyly and omphalocele (both around 10 times). An increased risk is seen also for gastroschisis but this is based on only 2 cases from the French registry and statistical significance is not reached.

For 2 malformations, there is a statistically significant difference between the 3 programs with respect to the proportion of DS with the malformation. One is median cleft palate—8 of 9 cases came from Sweden ($P = 0.015$); the other is megacolon where the rate is lower in Italy than in the other two programs ($P = 0.027$).

We found no statistically significant trend according to year of birth for duodenal atresia; other malformations were too few to permit such an analysis.

As seen in Table II, nearly all limb defects were of the transverse type. Only one case, missing fingers 4–5, could be regarded as a postaxial longitudinal deficiency.

Cardiac Malformations

The most common malformation in DS is a cardiac defect. In the present material, on average 26% of the infants had a cardiac defect: 23% from France, 21% from Italy, and 32% from Sweden. The higher rate in the Swedish material is probably due to the fact that all infants were followed-up to one year's age with data obtained from the child cardiology clinics. However, there is in all 3 programs a strong increasing trend in the rate of cardiac defects according to the year of birth. During the last 3 years of birth in each register, the rates were higher than for the total period. These years, 38% of DS had a cardiac defect in the French and Swedish registries and 25% in the Italian registry. Among the 57 stillborn DS, only 10 (17.5%) had a registered cardiac defect but the low rate may be random.

Table III shows the registered cardiac diagnoses. As expected, the most common cardiac defect was endocardial cushion defects (39%) followed by ventricular septum defect (28%) and atrial septum defect (7%). Tetralogy of Fallot or patent ductus were the leading malformation in between 3% and 4%; most infants with patent ductus had low birth weight. As much as 28% of all cardiac defects was unspecified: 19% among the Swedish cases,

TABLE II. Description of 10 Down Syndrome Infants With Limb Deficiency

Program	Year of birth	Missing skeletal parts
France	1978	One hand (side not specified)
	1982	2nd–3rd phalanges 3rd–45th fingers left hand
	1982	Left hand and wrist
	1987	Left hand (with "atrophic" left arm)
Italy	1979	Right hand
	1980	Right foot
	1982	Terminal phalanx right 2nd finger and left 3rd toe
	1985	Fingers 4–5 left hand
	1986	Right 2nd–3rd toes (with syndactyly 4th–5th)
Sweden	1990	2nd–4th finger left hand

25% among the French cases, and 44% among the Italian cases. These infants had received a diagnosis of a congenital cardiac defect but had not been further investigated at the time of reporting to the registries.

Maternal Age As a Risk Factor

We studied the maternal age (5-year classes) effect on the risk for the DS to have a malformation, stratifying for program. All other maternal age classes together were used as reference. Figure 2 shows the results for 4 relatively common malformations and for all cardiac defects and all noncardiac defects.

There is a slight trend towards an increased risk for an esophageal or anal atresia with maternal age, but the odds ratios are not significantly different from 1 in any class. If women below 30 and above 30 are compared (stratifying for program), an odds ratio of 0.77 with an exact 95% confidence interval of 0.50–1.16 is obtained. For duodenal atresia no trend is seen. For all cardiac malformations together, a statistically significant decrease of risk is seen in DS born to teenage mothers and this is still more pronounced for endocardial cushion defects and ventricular septum defects. For all noncardiac malformations together, no clear-cut effect of maternal age can be seen.

For less frequent malformations, data are shown in Table IV. Only 3 broad age groups are then studied. For all listed malformations with the exception of megacolon, no marked deviations between the observed and expected numbers are seen. For megacolon (a total of 31 cases with known maternal age), an increased risk for women below 25 is seen. If the group 25–34 years is used as a reference, the odds ratio (after stratification for program) was 2.58 with an exact 95% confidence interval of 1.08–6.26. The corresponding odds ratio for women aged 35 or more was 1.40 with a 95% confidence interval of 0.55–3.54.

TABLE III. Registered Cardiac Defects in Down Syndrome Infants

Cardiac defect	France	Italy	Sweden	Total	Percent of all
Single ventricle	0	0	2	2	0.1
Hypoplastic left heart	1	1	2	4	0.3
Truncus arteriosus	0	1	1	2	0.1
Transposition of great arteries	1	0	3	4	0.3
Endocardial cushion defect	152	109	290	551	38.5
Total anomalous return of pulmonary veins	0	0	1	1	0.1
Pulmonary atresia with intact ventricular septum	0	1	0	1	0.1
Tetralogy of Fallot	12	20	18	50	3.5
Coarctatio aortae	0	0	9	9	0.6
Ventricular septum defect	60	54	138	400	28.0
Aortic stenosis	0	1	0	1	0.1
Valvular pulmonary stenosis	1	2	0	3	0.2
Cardiomyopathy	0	1	0	1	0.1
Tricuspidal insufficiency	2	0	1	3	0.2
Vascular ring	1	0	2	3	0.2
Atrial septum defect	14	27	57	98	6.8
Patent ductus arteriosus	13	7	31	51	3.6
Other[a]	2	0	2	4	0.3
Total including unspecified	350	395	686	1,431	
% of all	22.5	20.9	32.1	25.6	

[a] Three infants with double orificium of the mitral valve and one unspecified pulmonary valve anomaly.

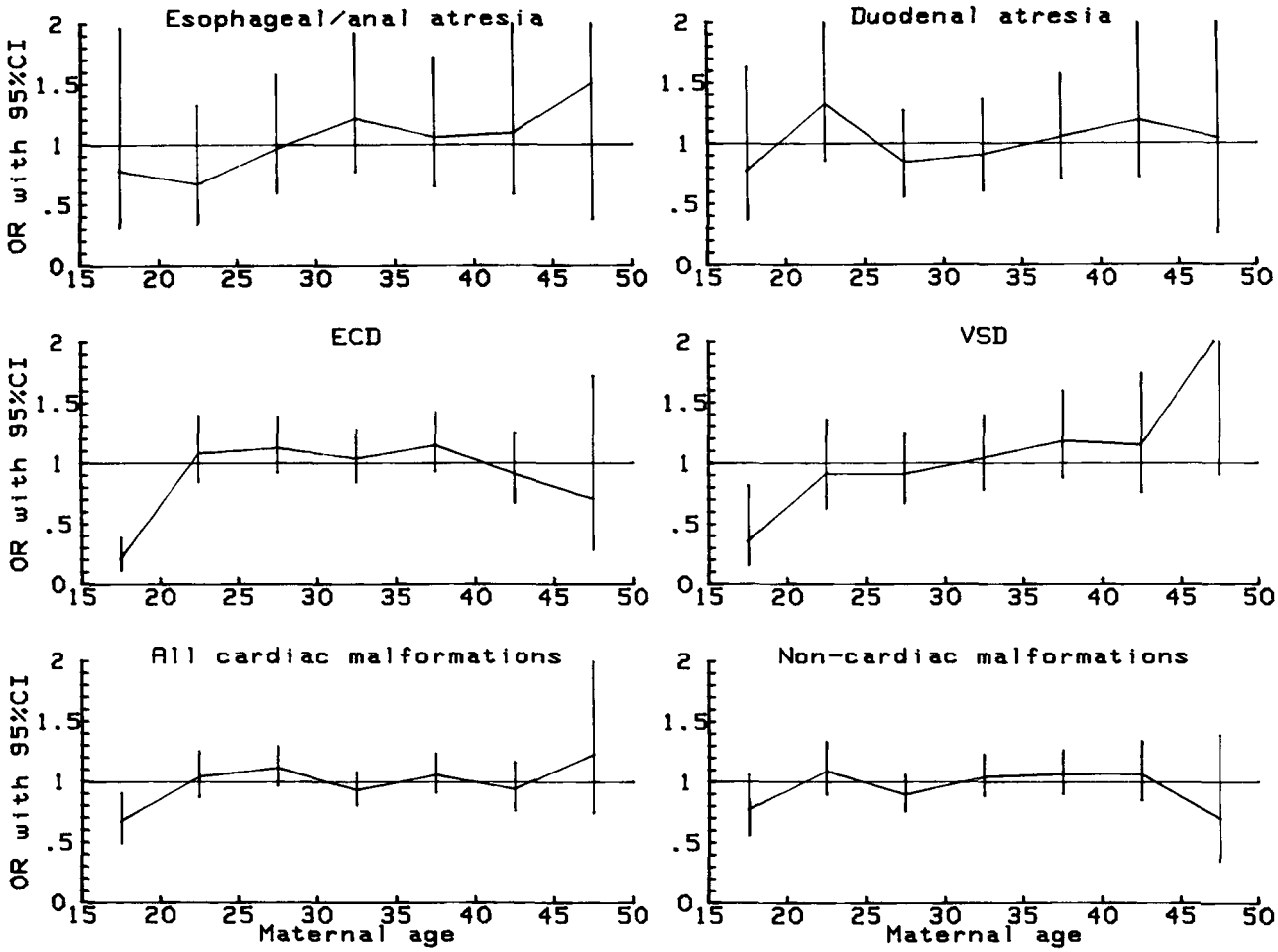

Fig. 2. Odds ratios (OR) with 95% confidence intervals (95% CI) for specific malformations at different maternal age classes. Each age class is compared with all other age classes. ECD = endocardial cushion defect; VSD = ventricular septum defect.

Infant Sex

Among all DS, 3,015 were male and 2,552 female (14 unknown sex); the sex ratio is thus 1.18, significantly above the population sex ratio of 1.06 ($\chi^2 = 15$, $P < 0.001$).

Table V demonstrates the sex distribution among DS with specific malformations and also the sex distribution among non-DS for each malformation. The sex ratios for specific malformations often differ between DS and non-DS but the former estimates are usually based on few cases only. As the sex ratio in DS is higher than in non-DS, comparisons were made as odds ratios for male in infants with a specific malformation versus infants without that malformation, first for the DS group, then for the non-DS with that malformation and recorded in the registers. Homogeneity between the 2 odds ratios was tested and in no instance was heterogeneity significant; the most marked degree of hetero-

TABLE IV. Maternal Age Distribution Among Infants With Down Syndrome and Some Specific Associated Malformations

	<25 years		25–34 years		≥35 years	
Malformation	Obs[a]	Exp[b]	Obs[a]	Exp[b]	Obs[a]	Exp[b]
Cataracts	5	2.4	5	7.2	5	5.4
Cleft lip or palate	4	3.9	10	12.5	11	8.5
Megacolon	12	6.7	10	14.6	9	9.7
Annular pancreas	3	4.2	13	13.0	11	9.7
Polydactyly, preaxial	3	2.6	6	6.0	4	4.4

[a] Observed.
[b] Expected, calculated from the total maternal age distribution of infants with Down syndrome after stratification for program.

TABLE V. Sex Distribution for Some Defects in Down Syndrome and in Non-Down Syndrome Infants

Malformation	Down			Non-Down		Odds ratio		
	M[a]	F[a]	SR[a]	SR	HO[b]	Down	Non-Down	Common OR[c]
Cataract	6	10	0.6	0.81	0.45	0.51	0.76	0.74 (0.58–0.95)
Cleft lip/palate	8	8	1.0	1.85	0.14	0.85	1.74	1.74 (1.63–1.85)
Cleft palate	7	2	3.5	0.80	0.07	2.96	0.76	0.76 (0.70–0.82)
Esophageal atresia	22	23	1.0	1.35	0.23	0.88	1.28	1.25 (1.11–1.42)
Duodenal atresia	75	63	1.2	1.13	0.59	1.01	1.06	1.05 (0.88–1.25)
Anal atresia	30	20	1.5	1.57	0.60	1.27	1.48	1.47 (1.31–1.66)
Megacolon	26	5	5.2	2.79	0.30	4.40	2.63	2.73 (2.15–3.47)
Annular pancreas	12	15	0.8	0.79	0.78	0.68	0.86	0.74 (0.40–1.17)
Omphalocele	6	2	3.0	1.20	0.31	2.54	1.13	1.14 (1.02–1.27)
Polydactyly	9	5	1.8	1.11	0.50	1.52	1.05	1.05 (0.93–1.18)
ECD[d]	268	281	1.0	0.72	0.21	0.81	0.68	0.75 (0.66–0.86)
ASD[d]	58	40	1.5	0.97	0.19	1.23	0.90	0.96 (0.81–1.13)
VSD[d]	115	137	0.8	0.95	0.09	0.71	0.90	0.87 (0.81–0.95)
Fallot tetralogy	31	19	1.6	1.38	0.85	1.38	1.30	1.31 (1.10–1.56)
PDA[d]	25	26	1.0	0.78	0.74	0.81	0.74	0.75 (0.60–0.93)

[a] M, males; F, females; SR, sex ratio.
[b] HO (test for homogeneity) gives P value in test for homogeneity between odds ratios for Down syndrome infants and non-Down syndrome infants.
[c] OR, odds ratio.
[d] ECD, endocardial cushion defect; VSD, ventricular septum defect; ASD, atrial septum defect; PDA, patent ductus arteriosus.

geneity was for cleft palate but the P value is 0.07 and thus not significant. A common odds ratio was then estimated after stratification for DS/non-DS and its 95% confidence interval was determined. It can be seen that some malformations (cleft lip/palate, esophageal atresia, anal atresia, megacolon, omphalocele, tetralogy of Fallot) show a significant male excess although not significantly different in DS and in non-DS. Cleft palate, endocardial cushion defect, and patent ductus all show significant female excess, but again there is no difference between DS and non-DS.

Karyotype

The rate of heart defects in DS without known karyotype was slightly lower (25%) than in DS with known karyotype (27%) but this difference can be random: odds ratio for a cardiac defect in the presence of a known karyotype versus absence of a known karyotype, stratified for maternal age, is 1.11 (95% CI 0.97–1.26). Cardiac defects were registered more often in translocation DS (30%) than in trisomy DS (27%), but the odds ratio, stratified for maternal age, is not significantly different from 1.0: OR = 1.17, 95% CI 0.80–1.71. In DS with mosaicism, cardiac defects occurred less often (19%) than in DS with trisomy (27%). The OR after stratification for maternal age was 0.54 but did not quite reach statistical significance; the 95% CI was 0.29–1.03.

The only other malformation with enough numbers to make such comparisons meaningful is duodenal atresia. DS with known karyotype had duodenal atresia slightly less often (2.4%) than DS with unknown karyotype (2.7%) but this may be random (OR = 0.91, 95% CI 0.64–1.31). In DS with translocations there were 4 subjects with duodenal atresia (3.0%) but the odds ratio versus DS with standard trisomy is not statistically significant: OR = 1.26, exact 95% CI 0.39–3.18. There were 2 mosaic DS with duodenal atresia (2.8%), again not significantly different from the occurrence in DS with standard trisomy: OR = 1.18, exact 95% CI 0.19–4.13.

DISCUSSION

The method of data collection probably underestimates the true rate of major malformations because cases are sometimes identified only by reports from cytogenetic laboratories where no information on concomitant malformations may be given. Cardiac defects or other malformations may be regarded as components of DS and therefore not reported. Some malformations, such as anencephaly, probably prevent the identification of DS. The rates of malformations recorded are therefore probably minimum; the total cardiac malformation rate (26%) is, for instance, lower than usually quoted (30–40%). A time trend existed for the rate of cardiac defects so it was higher than average among DS born during the last 3 years of the registration period, which probably indicates an increased ascertainment similar to that described by Khoury and Erickson [1992b]. No statistically significant such trend was seen for duodenal atresia, the only other malformation with large enough numbers to make such an analysis meaningful.

Another problem is that the follow-up time of the infants is sometimes short but may be longer in an infant with DS than in a normal infant, as the former may be observed longer at the neonatal ward and the probability to detect an internal malformation may increase. This can be demonstrated for megacolon. In France and Sweden, the rate of recorded megacolon among DS is roughly the same (0.7–0.8%) but the population rate in France (1.1 per 10,000) is more than twice that recorded in Sweden (0.5 per 10,000). In France, reporting extends to the age of 1 year, in Sweden it comprises little beyond the early neonatal period (except for cardiac defects). In Italy, the rate of megacolon in DS is lower than in the other 2 programs and the population rate (0.4 per 10,000) is similar to that found in Sweden and is also mainly based on perinatally detected cases. No aborted

fetuses with DS were included in the study. Prenatal diagnosis is nearly always based on karyotype only and this exclusion will therefore not bias the sample.

There may exist true population differences in the malformation rates among DS. The rate of recorded cleft lip/palate does not differ between the 3 programs, but the rate of recorded isolated cleft palate differs strongly: such cases were nearly exclusively found in the Swedish register. The population rate in Sweden is also somewhat higher (6.6 per 10,000) than in France and Italy (4.6 and 4.9 per 10,000, respectively) [ICBDMS, 1991].

We compared the rate of 20 malformations in DS with non-DS rates from the same populations. In many, the registered numbers are compatible with an absence of a risk increase. Sometimes this may be due to low numbers (e.g., microtia), but for hypospadias, for instance, the observed number of 10 is quite close to the expected number of 9.7. For some others, notably the facial clefts, a 3–4 times increase in rate is seen; for still others (omphalocele, esophageal and anal atresia) there is an even more marked increase. It is interesting that all these malformations are component manifestations also of the other 2 major trisomies, trisomy 18 and 13, where they occur at very high rates.

There are different possible explanations to an increased rate of a specific major malformation. One is the presence of a specific gene in the chromosome occurring in triplicate. Against this explanation is the fact that the same malformations are over-represented in all 3 trisomies (although to different degree). Another possible explanation is that the trisomic state unspecifically reduces the cell proliferation rate in early pregnancy and in this way increases the probability for maldevelopment. However, it is difficult to understand why some specific malformations should be the only ones sensitive to this process; one would rather have expected a generalized increase in rate in all types of major malformations. A third and intriguing possibility is that trisomy 21 increases the susceptibility of the embryo to teratogens, causing specific malformations. It is possible that DS with a specific malformation (e.g., an esophageal or anal atresia) should be compared with DS without such a malformation in studies of possible teratogenic exposures. However, in order to make such a study, extensive material is needed, which is possible to obtain only by extended international collaboration.

Khoury and Erickson [1992a] explored this idea in a small study of 219 infants with DS and studied, among other things, maternal age effect on the risk of an oral cleft, based on only 4 cases. They state an increased risk for women below age 25. Our study based on a 6 times larger sample does not confirm this observation. On the other hand, we found an indication of a maternal age effect on the risk that the DS had an esophageal or anal atresia. Such an age effect is also seen among infants with esophageal atresia and without chromosome anomalies, while the maternal age effect in anal atresia is U-shaped [Harris et al., 1995]. We found a significantly increased risk for the DS infant to have megacolon when the mother was below age 25 and a markedly reduced risk for cardiac defects (and notably endocardial cushion defects and ventricular septum defects) when the mother was a teenager. Obviously, maternal age effects may be indirect results of age-related exposures.

Many malformations show an aberrant sex ratio. We studied this problem comparing the sex ratios of infants with DS and a specific malformation and those of non-DS with the same malformation. We could detect no effect of the DS genotype on the sex specificity in malformations, neither in those with a male excess nor in those with a female excess. The female excess of cardiac defects seen at DS [Pinto et al., 1990] is thus due to the high proportion of endocardial cushion defects which in themselves have a female preponderance, and the presence of the DS genotype does not affect the sex ratio of that malformation. A homogeneity test of the data shown by Pinto et al. [1990] also supports the contention that the female preponderance does not significantly differ between DS and non-DS with endocardial cushion defects.

We found no statistically significant difference in the occurrence of cardiac defects or duodenal atresia in translocation and standard trisomy cases but we found a reduced rate of cardiac defects in mosaic cases even though statistical significance was not reached. Our material did not permit a comparison according to parental origin. A recent study of Stoll et al. [1995] found no evidence for a heterogeneity in DS phenotype according to parental origin but only 8 DS cases of paternal origin were included in the study.

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